Association Between Postoperative Hypoalbuminemia and Complications in Ovarian Carcinoma

Hypoalbuminemia and Complications

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Özet

Amaç: Yaş, performans durumu, cerrahi radikalite, nutrisyonel durum ve serum albumin düzeyi gibi birçok durum, artmış postoperatif komplikasyon için risk faktörü olarak tanımlanmıştır. Mevcut çalışmamızda amaç, postoperatif serum albumin düzeylerinin postoperatif komplikasyonlar üzerindeki etkisini araştırmaktır. Gereç ve Yöntem: Borderline over tümörü ya da invaziv over kanseri tanısı ile debulking cerrahisi yapılan hastalara ait veriler retrospektif olarak toplandı. Hafif hipoalbuminemi için eşik değer 3.5 g/dl, şiddetli hipoalbuminemi için eşik değer 2.5 g/dl olarak tanımlandı. Bulgular: Tarif edilen süre içerisinde debulking cerrahisi yapılan toplam 200 hasta tanımlandı. Şiddetli hipoalbuminemisi olan hastalarda daha fazla oranda ciddi komplikasyon izlendi (p<0.05, OR 2.6; 95% CI: 0.7-9.1). Ortalama diseke edilen lenf nodu sayıları şiddetli hipoalbuminemi, hafif hipoalbuminemi ve normal albumin seviyesine sahip hastalarda sırası ile 57.2, 49.4 ve 45.5 olarak tespit edildi (p<0.05). Şiddetli hipoalbuminemisi olan hastaların ortalama hastanede yatış süreleri (10.26 gün) ve yoğun bakımda kalış süreleri (1.5 gün), hafif hipoalbuminemisi olan hastalardan (sırası ile 9.3 gün ve 1.3 gün) ve normal albumin düzeylerine sahip hastalardan (sırasıyla 8.2 gün ve 1.2 gün) anlamlı olarak daha fazla idi (p<0.05). Şiddetli hipoalbuminemisi olan hastaların %60'ında, hafif hipoalbuminemisi olan hastaların %42.4'sinde ve normal albumin düzeylerine sahip hastaların %20'sinde eritrosit süspansiyonu transfüzyonu ihtiyacı olmuştur. Tartışma: Sonuç olarak, postoperatif hipoalbuminemi saptanan hastalar ciddi postoperatif komplikasyonlar açısından yüksek risklidir ve postoperatif dönemde daha yakın takip gereksinimleri olabilir.

Anahtar Kelimeler
Hipoalbuminemi; Debulking; Komplikasyon; Transfüzyon

Abstract

Aim: Several factors have been described as risk factors for increased postoperative complications, such as age, performance status, surgical aggressiveness, nutritional status, and serum albumin levels. The aim of the present study is to evaluate the predictive role of postoperative serum albumin levels on postoperative complications. Material and Method: Data of patients with the diagnosis of borderline ovarian tumors or invasive ovarian cancer and who had undergone debulking surgery were retrieved retrospectively. We defined the cut-off value of 3.5 g/dl for mild hypoalbuminemia and 2.5 g/dl for severe hypoalbuminemia. Results: A total of 200 patients were identified, all of whom had undergone debulking surgery at our hospital in the time period from January 2008 to December 2015. Patients with severe postoperative hypoalbuminemia had higher incidences of severe postoperative complications (CDC grade ≥2) (p<0.05, OR 2.6; 95% CI: 0.7-9.1). Mean dissected lymph node counts for patients with severe hypoalbuminemia, mild hypoalbuminemia, and normal albumin levels were 57.2, 49.4, and 45.5, respectively (P<0.05). Patients with severe hypoalbuminemia had longer hospital stays (mean 10.26 days) and ICU stays (mean 1.5 days) compared to patients with mild hypoalbuminemia (9.3 and 1.3 days, respectively) and those with normal albumin levels (8.2 and 1.2 days, respectively) (p<0.05). Sixty percent of the patients with severe hypoalbuminemia, 42.4% of the patients with mild hypoalbuminemia, and 20% of the patients with normal albumin levels needed at least one unit of packed RBC transfusion in the per-operative period. Discussion: Patients with postoperative hypoalbuminemia have an increased risk of serious postoperative complications and they should be more closely followed during the early postoperative course.

Keywords
Hypoalbuminemia; Debulking; Complication; Transfusion

Introduction

Primary cytoreductive surgery followed by adjuvant chemotherapy, if indicated, is the standard treatment for patients with ovarian carcinoma (OC) [1]. The key point of the surgical approach is to achieve maximal cytoreductive surgery with no gross residual tumor [2]. However, aggressive surgery is often associated with increased intraoperative and postoperative major complications and morbidity [3]. In addition, postoperative major complications may cause a delay in adjuvant chemotherapy following the cytoreductive surgery. Several factors have been described as risk factors for increased postoperative complications: age, performance status, surgical aggressiveness, nutritional status, and serum albumin levels [4,5]. Most of these factors cannot be measured with standardized quantitative methods.

Albumin is the major plasma protein in humans and has the major role in maintaining serum colloid pressure as well as acting as a transport vehicle for intrinsic metabolites, drugs, and anti-oxidative agents; it acts as a free-radical scavenger [6]. Preoperative low serum albumin level has been associated with increased postoperative major complications and morbidity for various types of oncological surgery [7-9]. Albumin level is also an indicator of malnutrition in patients. A significant percentage of patients with gynecological malignancy have malnutrition (20%), but ovarian cancer patients have the highest prevalence of malnutrition (67%) [10]. Previous studies have been focused on preoperative serum albumin status as a predictor. However, the aim of the present study is to evaluate the predictive role of postoperative serum albumin levels on postoperative complications, as categorized by Clavien-Dindo Classification (CDC).

Material and Method

The present study is designed as a retrospective cohort study. Data of the patients who had been operated on at our tertiary-care referral hospital from January 2008 to December 2015 were retrieved from computerized databases and patient files. Diagnoses of the patients were either OC or borderline ovarian tumors (BOT). Both groups of patients underwent cytoreductive surgery of staging including removal of at least one adnexa, infragastric or infracolic omentectomy, and retroperitoneal lymph node dissection up to the renal veins. Those patients without complete surgical staging were excluded from the study. The standard surgical approach for epithelial ovarian carcinoma (EOC) was maximal cytoreductive surgery, whereas BOTs and other OC subtypes were managed according to the patients' ages and fertility desire. The surgeries were performed by a surgical team specialized in gynecological oncology. Patients who received neo-adjuvant chemotherapy were excluded. Serum albumin levels were measured on postoperative day 1 as a routine postoperative follow-up.

Serum albumin was assayed with bromocresol green, using routine clinical chemical photometric analyzers. We defined the cut-off value of 3.5 g/dl for mild hypoalbuminemia and 2.5 g/dl for severe hypoalbuminemia. Postoperative complications were classified according to CDC [11] including the hospital stay period. According to these criteria, the complications were further stratified as mild (CDC 0-1) or severe (CDC 2-4). Higher CDC scores were noted in those patients with multiple complications

or more severe complications.

Descriptive statistics were presented as mean, median, and percentages. Fisher-exact and Pearson correlation tests were used to assess the relationship between continuous variables such as complications and serum albumin levels. Albumin levels were labeled as severe hypoalbuminemia, mild hypoalbuminemia, and normal serum albumin levels, to create categorical variables for univariate and multivariate analyses. Cox logistic regression model was used for univariate analyses. P values <0.05 were considered statistically significant. Statistical software SPSS 21 for Macintosh (SPSS 21, SPSS Inc., Chicago, IL) was used for statistical analysis.

We have obtained the Institutional Review Board approval for the present study. [Date and number: 31.07.2015#14]

Results

A total of 200 patients were identified as having undergone debulking surgery or staging surgery for ovarian tumors in the time period from January 2008 to December 2015. Patient characteristics are shown in Table 1. The median age of the

Table 1. Patient characteristics of women with ovarian tumors undergoing primary cytoreductive surgery

Variable	N	%
All patients	200	
Age — median (range, years)	53 (18-81)	
Day 1 Albumin (g/dL) — mean (SD)	2.77 (±0.5)	
≤2.5 g/dL	60	30
2.5-3.5 g/dl	125	
>3.5 g/dL	15	5.5
Final Pathology		
EOK	124	62
SCST	25	12.5
GCT	10	5
BOT	41	20.5
Surgical Procedure		
Fertility sparing	28	14
Debulking	172	86
Dissected LN count (median, range)	52 (5-200)	
Disease Stage (FIGO)		
1A	56	28
1B	10	5
1C (C1, C2, C3)	21	10.5
2A	11	5.5
2B	31	15.5
3A (3A1, 3A2)	57	28.5
3B	2	1
3C	5	2.5
4A/B	6	3

EOK: Epithelial ovarian cancer; SCST: Sex-cord stromal tumor; GCT: Germ cell tumor; BOT: Borderline ovarian tumor; LN: Lymph node

patients was 53 (ranging between 18-81). One hundred twenty-four patients (62%) had epithelial OC, 25 patients (12.5%) had sex-cord stromal tumors, 10 patients (5%) had germ cell tumors, and 41 patients (20.5%) had BOTs. Twenty-eight patients (14%) had fertility sparing staging surgery, whereas remaining 172 patients (86%) had complete debulking surgery. Seventy

patients (35%) had advanced stage disease (FIGO 3A-4). According to the inclusion criteria, all patients had bilateral pelvic and para-aortic lymph node dissection. Median dissected lymph node count was 52 (range 5-200). Sixty patients (30%) had serum albumin levels lower than 2.5 g/dl representing severe hypoalbuminemia, while 125 (62.5%) patients had serum albumin levels between 2.5-3.5 g/dl representing mild hypoalbuminemia, and the other 15 (7.5%) patients had normal serum albumin levels, >3.5 g/dl on postoperative day 1. Mean hospitalization duration was 9.9 days (range 5-35 days) and the median ICU stay was 1 day (range 1-33 days). One patient had 33 days of ICU stay, and we excluded this patient from descriptive analysis of ICU and hospital stay. A total of 104 patients had serious postoperative complications of CDC grade 2 or higher. The patients with severe postoperative hypoalbuminemia (serum albumin level <2.5 g/dl), had a higher incidence of severe postoperative complications (CDC grade ≥2) (p<0.05, OR 2.6; 95% CI: 0.7-9.1) compared to patients with normal albumin levels. Among 60 patients with severe hypoalbuminemia, 40 (66%) of them experienced severe postoperative complications. Also, patients with mild hypoalbuminemia (serum albumin level 2.5-3.5 g/dl) had a higher incidence of CDC grade ≥2 complications compared to patients with normal serum albumin on postoperative day 1 (p<0.05, OR 1.7; 95% CI: 0.6-5.1). Among 125 patients with mild hypoalbuminemia, 60 (48%) of them experienced CDC grade ≥2 complications compared to 4 of 15 (26.6%) patients with albumin levels ≥3.5 g/dl.

Mean dissected lymph node counts were inversely related with serum albumin status. Mean dissected lymph node counts were 57.2, 49.4, and 45.5 for patients with severe hypoalbuminemia, mild hypoalbuminemia, and normal albumin levels, respectively (P<0.05).

The patients with postoperative severe hypoalbuminemia had longer hospital stays (mean 10.26 days) and ICU stays (mean 1.5 days) compared to patients with mild hypoalbuminemia (9.3 and 1.3 days, respectively) and when compared to patients with normal albumin levels (8.2 and 1.2 days, respectively) (p<0.05). One hundred-eight patients had red blood cell (RBC) transfusion, while the remaining 92 patients did not need RBC transfusion; postoperative hypoalbuminemia was significantly related with the need for RBC transfusion. Thirty-six of 60 patients (60%) with severe hypoalbuminemia, 53 of 125 patients (42.4%) with mild hypoalbuminemia, and only three of 15 patients (20%) with normal albumin levels needed at least one unit of packed RBC transfusion in the per-operative period (P<0.05, OR 2.8; 95% CI: 0.8-4.9 and 2.2; 95% CI: 0.7-4.1 for patients with severe and mild hypoalbuminemia, respectively, compared to patients with normal serum albumin levels). The postoperative complications were further categorized as pulmonary complications, renal failure and electrolyte imbalance, thromboembolic complications, wound complications, sepsis, gastrointestinal complications, surgical complications and cardiac complications. Postoperative hypoalbuminemia was not associated with any specific organ system complications (Table 2).

Discussion

Hypoalbuminemia is a well-known indicator of malnutrition, and an association between hypoalbuminemia, inflammation,

Table 2.

Variable	Postoperative Albumin			p	OR (%95 CI)
	<2.5 g/dl N=60	2.5-3.5 g/dl N=125	>3.5 g/dl N=15		
Mean dissected lymph node count	57.2	49.4	45.5	<0.05	NA
Serious postoperative complications (CDC2+)					
Yes (%)	40 (66%)	60 (48%)	4 (26.6%)	<0.05	
No (%)	20 (33%)	65 (52%)	11 (73.3%)		
OR	2.6	1.7	Ref		
Number of serious post-operative complications (mean)	0.33	0.14	0.07	<0.05	NA
Need for transfusion					
Yes (%)	36 (60%)	53 (42.4%)	3 (20%)	0.002	
No (%)	24 (40%)	72 (57.6%)	12 (80%)		
OR	2.8	2.2	Ref.		
Hospital stay (days, mean, median)	10.2, (10)	9.3, (8)	8.2, (7)	<0.05	
ICU stay (days, mean, median)	1.5 (2)	1.3 (1)	1.1 (1)	<0.05	

CDC: Clavien-Dindo Classification; ICU: Intensive Care Unit; OR: Odds Ratio

and malignancy has been recently suggested [12]. Preoperative low serum albumin level was shown to have a major impact on surgical outcome, length of hospital stay and postoperative complications, especially in radical gastrointestinal surgeries [13,14]. Uppal et al. showed a six times elevated risk of major postoperative complications and ten times more likelihood of death in the first 30 postoperative days for patients with preoperative hypoalbuminemia in their patient cohort, which consisted of 2110 gynecologic oncology patients [7].

Seebacher et al. investigated the impact of preoperative hypoalbuminemia on survival in their retrospective cohort of 465 endometrial cancer patients [9]. The authors found that preoperative low albumin levels were strongly associated with advanced stage disease, a higher histologic grade, and poor survival. However, the authors could not determine a clear prognostic cut-off value for serum albumin.

For advanced stage epithelial ovarian cancer patients, Aletti et al. showed ASA score, tumor grade, surgical complexity, and preoperative low albumin levels were independent risk factors for postoperative complications [15]. Similarly, Obermair et al. demonstrated a significant increase in anastomose failure and septic complications in patients with hypoalbuminemia who underwent bowel resection as part of cytoreduction in advanced stage ovarian cancer [16].

In a recent study, Ataseven et al. investigated the association between preoperative hypoalbuminemia and postoperative complications in 604 EOC patients [17]. The authors concluded that patients with hypoalbuminemia were five times more likely to develop serious postoperative complications than patients with normal serum albumin levels. Moreover, median survival of patients with low albumin levels and normal albumin levels were 24 and 83 months, respectively.

The possible explanation of the relationship between hypoalbu-

minemia and severe postoperative complications could be that low serum albumin is a strong predictor of malnutrition [18], cachexia, and chronic inflammatory process [19]. Moreover, cancer related cachexia is associated with immunosuppression [20], which has been reported as a predictor for severe postoperative complications [4] and poor survival [8].

It is not well understood whether hypoalbuminemia causes a worse prognosis because it only reflects malnutrition or if it directly and independently influences the patient's prognosis [17]. Improving the nutritional status of ovarian cancer patients with low serum prealbumin levels through total parenteral nutrition prior to surgery is associated with fewer postoperative complications [4]. However, subsequent randomized trials failed to show the benefit of preoperative nutritional therapy on complication rates [21,22].

Most studies in the literature investigate the association between preoperative low albumin levels and postoperative morbidity. However, our study attempts to demonstrate the additional importance of early postoperative low albumin levels. In our study population, serum albumin levels on postoperative day 1 were ≤3.5 g/dL in a majority of patients and this was associated with more severe complications (≥CDC grade 2), longer ICU administration, and longer hospital stays.

Albumin level is a predictor of malnutrition, as well as a well-known negative acute phase reactant. Serum albumin levels decrease rapidly in response to acute inflammatory cytokines [23]. The association between postoperative hypoalbuminemia and postoperative morbidity is probably due to the negative acute phase reactant nature of the albumin, rather than its being a predictor for malnutrition. Also, a minority of the patients in our study had advanced stage and bulky disease (stage 3C and 4), thus indicating cancer cachexia.

The main limitation of our study is the retrospective design of the study that leads to selection bias and heterogeneity of patients and procedures. In addition, there is no cut-off value for early postoperative serum albumin level in the literature.

In our patient cohort, postoperative albumin levels were inversely related with postoperative complication rates, blood transfusion rates, and the duration of hospital and ICU stays of the patients. Postoperative low albumin levels seem to be related with surgical complexity rather than nutritional status. This is due to the negative acute phase reactant nature of the albumin. The patients with postoperative hypoalbuminemia should be more closely followed-up during the early postoperative course.

Competing interests
The authors declare that they have no competing interests.

References

1. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009;115(6):1234-44.
2. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20(5):1248-59.
3. Aletti GD, Eisenhauer EL, Santillan A, Axtell A, Aletti G, Holschneider C et al. Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. Gynecol Oncol 2011;120(1):23-8.
4. Geisler JP, Linnemeier GC, Thomas AJ, Manahan KJ. Nutritional assessment using prealbumin as an objective criterion to determine whom should not undergo primary radical cytoreductive surgery for ovarian cancer. Gynecol Oncol 2007;106(1):128-31.
5. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol 2007;197(6):676 e1-7.
6. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. Mol Aspects Med 2012;33(3):209-90.
7. Uppal S, Al-Niaimi A, Rice LW, Rose SL, Kushner DM, Spencer RJ et al. Preoperative hypoalbuminemia is an independent predictor of poor perioperative outcomes in women undergoing open surgery for gynecologic malignancies. Gynecol Oncol 2013;131(2):416-22.
8. Asher V, Lee J, Bali A. Preoperative serum albumin is an independent prognostic predictor of survival in ovarian cancer. Med Oncol 2012;29(3):2005-9.
9. Seebacher V, Grimm C, Reinthaller A, Heinze G, Tempfer C, Hefler L et al. The value of serum albumin as a novel independent marker for prognosis in patients with endometrial cancer. Eur J Obstet Gynecol Reprod Biol 2013;171(1):101-6.
10. Laky B, Janda M, Cleghorn G, Obermair A. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. Am J Clin Nutr 2008;87(6):1678-85.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205-13.
12. Al-Shaiba R, McMillan DC, Angerson WJ, Leen E, McArdle CS, Horgan P. The relationship between hypoalbuminaemia, tumour volume and the systemic inflammatory response in patients with colorectal liver metastases. Br J Cancer 2004;91(2):205-7.
13. Lohsiriwat V, Lohsiriwat D, Boonnuch W, Chinswangwatanakul V, Akaraviputh T, Lert-Akayamanee N. Pre-operative hypoalbuminemia is a major risk factor for postoperative complications following rectal cancer surgery. World J Gastroenterol 2008;14(8):1248-51.
14. Lai CC, You JF, Yeh CY, Chen JS, Tang R, Wang JY et al. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. Int J Colorectal Dis 2011;26(4):473-81.
15. Aletti GD, Santillan A, Eisenhauer EL, Hu J, Aletti G, Podratz KC et al. A new frontier for quality of care in gynecologic oncology surgery: multi-institutional assessment of short-term outcomes for ovarian cancer using a risk-adjusted model. Gynecol Oncol 2007;107(1):99-106.
16. Obermair A, Hagenauer S, Tamandl D, Clayton RD, Nicklin JL, Perrin LC et al. Safety and efficacy of low anterior en bloc resection as part of cytoreductive surgery for patients with ovarian cancer. Gynecol Oncol 2001;83(1):115-20.
17. Ataseven B, du Bois A, Reinthaller A, Traut A, Heitz F, Aust S et al. Pre-operative serum albumin is associated with post-operative complication rate and overall survival in patients with epithelial ovarian cancer undergoing cytoreductive surgery. Gynecol Oncol 2015;138(3):560-5.
18. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F et al. ESPEN Guidelines on Parenteral Nutrition: surgery. Clin Nutr 2009;28(4):378-86.
19. Khuri SF, Daley J, Henderson W, Hur K, Gibbs JO, Barbour G et al. Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 1997;185(4):315-27.
20. Yazawa T, Shibata M, Gonda K, Machida T, Suzuki S, Kenjo A et al. Increased IL-17 production correlates with immunosuppression involving myeloid-derived suppressor cells and nutritional impairment in patients with various gastrointestinal cancers. Mol Clin Oncol 2013;1(4):675-9.
21. Hubner M, Cerantola Y, Grass F, Bertrand PC, Schafer M, Demartines N. Preoperative immunonutrition in patients at nutritional risk: results of a double-blinded randomized clinical trial. Eur J Clin Nutr 2012;66(7):850-5.
22. Fujitani K, Tsujinaka T, Fujita J, Miyashiro I, Imamura H, Kimura Y et al. Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer. Br J Surg 2012;99(5):621-9.
23. Moshage HJ, Janssen JA, Franssen JH, Hafkenscheid JC, Yap SH. Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation. J Clin Invest 1987;79(6):1635-41.